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Pd-Catalyzed and Copper Assisted Regioselective Sequential C2 and C7 Arylation of Thiazolo[5,4-*f*]quinazolin-9(8*H*)-one with Aryl Halides

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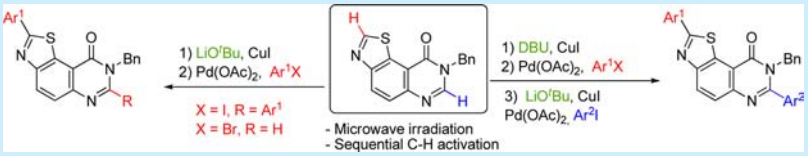
Supporting Information



ABSTRACT: A selective functionalization of thiazolo[5,4-*f*]quinazolin-9(8*H*)-one has been developed through sequential activation of C−H bonds to furnish diarylated compounds. This strategy allows the regioselective C2 and C7 arylation by a judicious choice of coupling partners and bases, requiring no additional ligands or directing groups. Differently substituted N^8-benzylated-2,7-diaryl-thiazoloquinazolin-9(8*H*)-ones were thereby obtained in a facile manner. A one-pot procedure was also performed. These protocols provide a synthetically useful route for late-stage functionalization of this highly valuable scaffold, required in drug discovery.

The development of a process for selective and sequential building of C−C bonds remains a significant challenge for organic chemists, especially for the functionalization of *N*-bearing ubiquitous cyclic frameworks.[1] In this context, transition-metal-catalyzed C−C coupling of a heteroarene through C−H arylation represents an extremely attractive approach.[2] This methodology has emerged as an important tool for incorporating structural diversity into complex nitrogen containing heterocycles, without the need for prefunctionalized starting materials, useful in drug discovery.[3] The emergence of direct functionalization strategies for heteroaromatics allows us to assess the potential for selective C−H functionalization in the 6,6,5-tricyclic-thiazolo[5,4-*f*]-quinazolin-9(8*H*)-one scaffold. This heterocycle was used as a versatile molecular platform for the synthesis of various derivatives with broad applications in biological sciences.[4,5] Our research group was focused on the synthesis of a novel thiazolo[5,4-*f*]quinazolin-9(8*H*)-one library as potential kinase inhibitors. We previously reported that thiazolo[5,4-*f*]quinazolin(-on)e derivatives displayed single-digit nanomolar IC_{50} values and are among the most potent DYRK1A/1B inhibitors disclosed to date (compounds **I** and **II**, Figure 1).[6] The ability to perform selective functionalization on thiazolo[5,4-*f*]quinazolin-9-one derivatives would considerably facilitate novel library synthesis that is essential for drug discovery. Since both the linear and angular isomers have pharmacological activity, general synthetic strategies are highly desirable for functionalization of theses valuable heterocycles. The synthesis of a series of diarylated thiazolo[5,4-*f*]quinazolin-9(8*H*)-ones as potential kinase inhibitors described by structure **A** is envisioned (Figure 1).

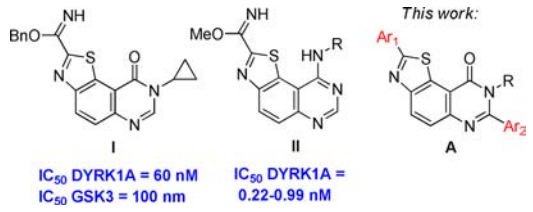


Figure 1. Structures of molecule hits **I** and **II**.

Despite their obvious synthetic interest, there are significantly less examples reported of diarylation of heteroarenes involving a stepwise or one-pot sequential strategy using aryl halides.[7] Given that selective C−H arylation is an ideal strategy for late-stage functionalization, we opted to use the N^8-benzylated-thiazolo-quinazolin-9(8*H*)-one **1** as the substrate, a key structural unit in the DYRK1 kinase inhibitor series. At the start of our study, the reaction was based on our reported results on C2−H arylation of quinazolin-4-ones and pyridopyrimidin-ones[8] under microwave irradiation.[9] Under these conditions, no selective C7−H phenylated product was observed (Table 1, entry 1). These reaction conditions afforded a mixture of C2-mono- and C2/C7-bis-phenylated products **2a** and **3a**, among starting material **1**. However, when the loading of aryl iodide was increased and the reaction time was prolonged to 5 h, diphenylated product **3a** was interestingly obtained in up to 68% yield (Table 1, entry 6). Notably, products **2a** and **3a** are readily separated by flash column chromatography on silica gel.

In order to improve selective C2−H arylation on the thiazole part, the reaction was performed without CuI (Table 1, entry 2). According to our previous study on arylation of quinazolin-4-one,[8] product **3a** was effectively not obtained. However, starting material was recovered as the major compound and **2a** was isolated in only 30% yield. To circumvent the limitation of

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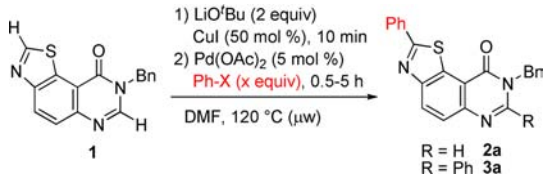
Table 1. C−H Arylation of N^3-Benzylated-Thiazolo[5,4-*f*]quinazolin-9(8*H*)-one 1 with Aryl Halide[a]



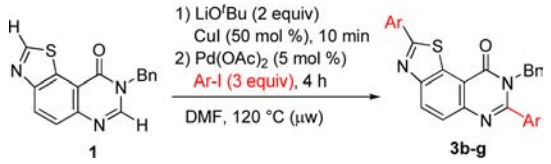
entry	time (h)	PhX (*x* equiv)	**2a** (yield %)[b]	**3a** (yield %)[b]
1	0.5	PhI (2)	27	45 (23)[c]
2[d]	1	PhI (2)	30	0 (64)[c]
3	4	PhI (2)	28	53 (0)[c]
4	4	PhI (3)	32	59 (0)[c]
5[e]	4	PhI (3)	31	62 (0)[c]
6	5	PhI (4)	27	68 (0)[c]
7	3	PhBr (2)	93	0 (0)[c]
8	3	PhCl (2)	0	0 (100)[c]

[a]Conditions: Reactions were performed in a sealed tube at 0.4 M with premixing CuI (50 mol %), LiO*t*Bu (2 equiv), and **1** (1 equiv) in a microwave reactor, before adding PhX (*x* equiv), Pd(OAc)$_2$ (5 mol %). [b]Reported yields are isolated yields. [c]Yields of recovered starting material **1**. [d]The reaction was performed without CuI. [e]The reaction was performed with 1 equiv of CuI.

C−H activation selectivity, we considered that switching the coupling partner for phenyl bromide or chloride could lead exclusively to a C2-phenylated compound. While compound **2a** was selectively obtained in excellent yield using phenyl bromide, no reaction occurred with phenyl chloride (Table 1, entries 7−8). The reaction was complete at 120 °C under microwave irradiation within 3 h based on TLC monitoring.

With acceptable conditions established, we explored first the scope of the bis-arylation reaction (Table 2) with various aryl

Table 2. Scope of Bis-arylation Reactions[a]



entry	Ar-	compd	yield (%)[b]
1	4-Me-Ph-	**3b**	63 (30)[c]
2	4-MeO-Ph-	**3c**	67 (29)[c]
3	4-Cl-Ph-	**3d**	56 (41)[c]
4	4-F-Ph-	**3e**	26 (58)[c]
5	4-CN-Ph-	**3f**	55 (38)[c]
6	2,4-Cl-Ph-	**3g**	0 (88)[c]

[a]Conditions: Reactions were performed in a sealed tube at 0.4 M with premixing **1** (1 equiv), LiO^{t}Bu (2 equiv), and CuI (50 mol %) in a microwave reactor, before adding ArI (3 equiv), Pd(OAc)$_2$ (5 mol %). [b]Reported yields are isolated yields. [c]Isolated yields of corresponding compound **2b−g**.

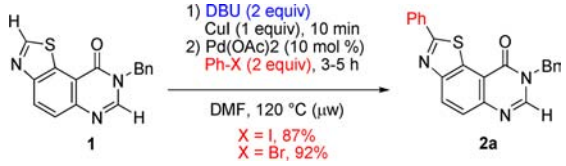
iodides. When aryl iodide was introduced, the resulting 2-aryl-thiazolo[5,4-*f*]quinazolin-9(8*H*)-ones were reactive enough to perform a second arylation, yielding significant amounts of 2,7-homodiarylated products **3b−f**. This double C2/C7 arylation protocol yielded targeted compounds in moderate yields. Whatever the applied reaction conditions, the bis-arylation was not complete and compounds **2a−g** were isolated even with a longer reaction time.

When the reaction was conducted with 2,4-dichlorophenyl iodide, the bis-arylated product was not obtained (entry 6). As previously described,[8a] experimentation involving an *ortho*-substituent with an electronic effect was unsuccessful on the quinazolinone part.

For structure−activity relationship (SAR) studies, the development of an efficient regioselective functionalization based on sequential C−H arylation is required. Despite the clear interest in selective C2−H arylation, this developed methodology is limited to aryl bromides as the coupling partner. In this regard, a convenient protocol allowing the use of aryl iodides as coupling partners is still required to extend the scope of the reaction. Inspired by recent reported studies on the arylation of benzothiazoles, we postulated that the selective C2−H activation could be performed by using copper and/or palladium catalysts.[10] One of the most attractive methods for C−H arylation of benzothiazole unit was reported by Daugulis, who used a CuI catalyst in the presence of *t*BuOLi as a base.[10b] Under these conditions, C2-phenylated product **2a** was obtained in only 28% yield. Whereas an increased amount of CuI or addition of ligand did not improve the efficiency of the reaction, better conversion was observed with a longer time.[11] Unfortunately, starting material **1** was not completely consumed after 4 h under microwave irradiation making the sequential CH arylation approach difficult to apply. Since only *t*BuOLi was effective for the C−H arylation of the quinazolin-4-one part,[8a] we finally improved the C2−H arylation of the azole moiety by switching the base.

After the extensive screening of various reaction parameters, it was found that addition of 1.0 equiv of CuI in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[12] dramatically improved the reaction efficiency.[11] The selective arylation took place at the most acidic C2−H site. A longer reaction time and 10 mol % Pd(OAc)$_2$ are required for a total conversion of **1**. Under these conditions, both phenyl iodide and bromide are effective as coupling partners to afford C2-phenylated compound **2a** in 87% and 92% yield, within 3 and 5 h, respectively (Scheme 1). With the optimum reaction conditions in hand, the scope of the stepwise arylation reaction of **1** was examined. The results were depicted in Schemes 2 and 3.

Scheme 1. Regioselective C2−H Arylation with DBU



The selective C2 arylation is effective for electron-neutral and electron-rich aryl iodides or bromides, containing methyl, methoxy, dimethylamino, fluorine, and chlorine substituents (**2b−e**; **2h**, 59−87%). Electron-deficient aryl iodides and azine rings gave monoarylated products **2f** and **2i−j** in 47−69% yield. In addition, we were pleased to see that *β*-bromostyrene was also an effective coupling partner as demonstrated by the alkenylation reaction leading to compound **2k** (Scheme 3). The moderate yield of compound **2k** is arguably due to the degradation of the bromostyrene reagent at high temperature in highly polar DMF solvent.

We then turned our attention to the synthesis of diarylated compounds. For this purpose, compound **2a** was submitted to

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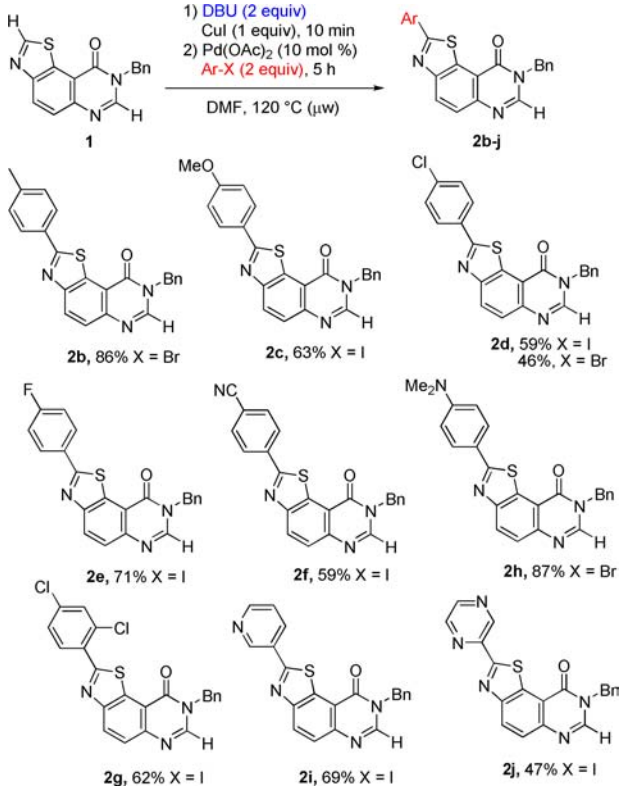
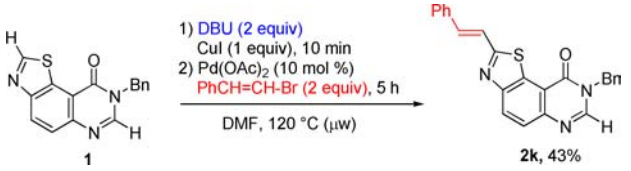
Scheme 2. Scope of the C2 Arylation of N^3-Benzylated-Thiazolo[5,4-*f*]quinazolin-9(8*H*)-one 1 with Aryl Halides[a]



[a]Premixing **1** (1 equiv), DBU (2 equiv), and CuI (1 equiv), before adding ArI or ArBr (2 equiv), $Pd(OAc)_2$ (10 mol %) for 5 h.

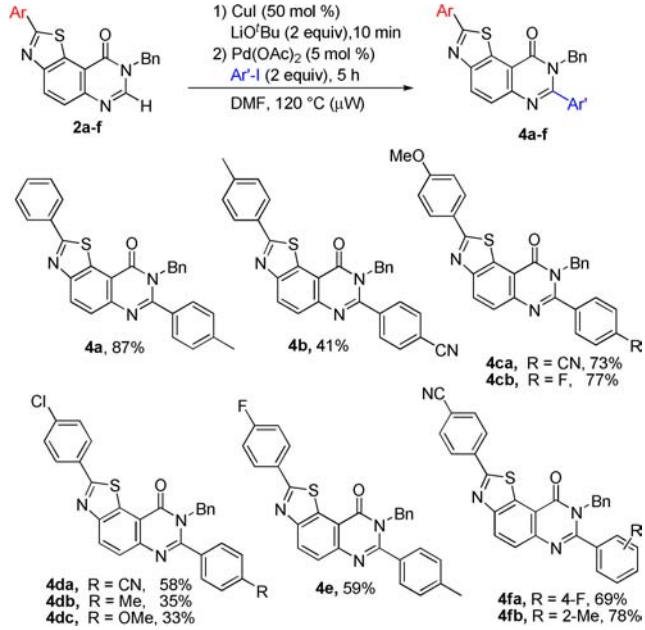
Scheme 3. C2 Alkenylation of Thiazolo[5,4-*f*]quinazolin-9(8*H*)-one 1 with *β*-Bromostyrene



the previously reported conditions for C−H arylation of quinazolinones.[8a] Under these aforementioned conditions, compound **2a** was further successfully arylated at C7 on the quinazolin-4-one (Scheme 4) to afford diarylated compound **4a** in 87% yield after 5 h. We subsequently carried out the C7-arylation of compounds **2b−f** with aryl iodides bearing a methyl, methoxy, fluoro, or cyano substituent at the *para*- or *ortho*-position (Scheme 4).

Diverse aryl groups are readily introduced into the quinazolinone part of compounds **2a−f** in acceptable yields. The 4-cyano-phenyl iodide is of particular note and led to compounds **4b−da** in yields up to 73%. The arylation of compound **2f** was also efficient, and compounds **4fa** and **4fb** were obtained in 69% and 78% yield, respectively. An electron-neutral substituent such as methyl in the *ortho*-position of the coupling partner was found to be suitable. In some cases, the reaction is not complete and the starting material was also recovered. In addition, compounds **4** are especially difficult to purify owing to their low solubility. It was noted that the arylation of the 2-arylbenzothiazole moiety of compounds **2b−f** that afforded an undesired product was not observed.[13] The

Scheme 4. Regioselective C7 Arylation of 2-Aryl-N^3-Benzylated-Thiazolo[5,4-*f*]quinazolin-9(8*H*)-ones 2a−f[a]

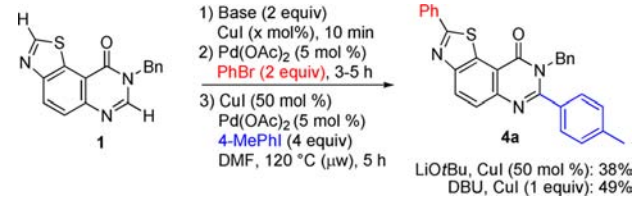


[a]Premixing **2** (1 equiv), LiO*t*Bu (2 equiv), and CuI (50 mol %), before adding ArI (2 equiv), $Pd(OAc)_2$ (5 mol %) for 5 h.

stepwise Pd-catalyzed C−H arylation of thiazolo[5,4-*f*]-quinazolin-9(8*H*)-one **1** with aryl bromides and iodides occurs in an efficient manner with broad tolerance to substituents on the coupling partners. The challenging removal of the protecting group was investigated, but many of the standard debenzylation strategies failed.[4a,14]

We then envisioned the dual C−H bond functionalization in a one-pot process, allowing the chromatographic purification step to be discarded. The first C2-arylation of compound **1** with phenyl bromide was complete within 3 or 5 h, depending on the base. The second arylation was finally achieved by the *in situ* addition of tolyl iodide, CuI (50 mol %), and $Pd(OAc)_2$ (5 mol %) to the reaction mixture and led to the expected C2 and C7 diarylated thiazolo[5,4-*f*]quinazolin-9(8*H*)-one **4a** in acceptable yield (Scheme 5).

Scheme 5. Ligand Free One-Pot Sequential C2 and C7 Arylation of N^3-Benzylated-Thiazolo[5,4-*f*]quinazolin-9-(8*H*)one 1



In conclusion, we have developed a mild and efficient functionalization of N^3-benzylated-thiazoloquinazolin-9(8*H*)-one based on sequential selective C−H arylation. This procedure tolerates a wide variety of substituents on the aryl halides. Electron-deficient heteroarenes are also readily introduced at the C2 position, a notable feature with respect to medicinal agent synthesis. Thiazoloquinazolin-9(8*H*)-one proved to be a viable substrate for C−H (hetero)-arylation,

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providing easy routes for late-stage structural diversification of this high valuable nitrogen containing heterocycle. The introduction of an aryl group upon the heteroarene core usually modifies the bioactivity profile of the molecule compared to the parent compound. Brief studies of their structure−activity relationships as kinase inhibitors will be realized in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01552.

Experimental procedures and characterization for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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